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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 17

Application Number: 09/419,328
Filing Date: October 15, 1999
Appellant(s): ROOK, ALAIN H.

Jane Massey Licata
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on 19 June 2002.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existance of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1 and 3 under 35 U.S.C. 103(a) stand or fall together as acknowledged by the appellant in the brief, and the other rejections of claims 1, 3 and 4 apply to a single claim each.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is incorrect, and it is the amended version made in response to the final Office Action, and the

amendment is ***not*** entered. For the purpose of appeal, the previous version of the claims without the after final amendment is provided as the following:

Claim 1. A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human an effective amount of recombinant interleukin-12 in a pharmaceutically acceptable carrier.

Claim 3. A composition for treatment of advanced cutaneous T cell lymphoma in a human comprising recombinant interleukin-12 and an adjunct therapeutic agent which stimulates interferon-γ production, said adjunct therapeutic agent comprising a retinoid, interleukin-18, interferon-α or interferon-γ.

Claim 4. A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human an effective amount of recombinant interleukin-12 in a pharmaceutically acceptable carrier and an adjunct therapeutic agent which stimulates interferon-γ production.

(9) Prior Art of Record

Rook et al., Pathogenesis of cutaneous T-cell lymphoma: implications for the use of recombinant cytokines and photopheresis. Clin. Exp. Immunol., 1997 January, 107 Suppl 1: 16-20.

Rook et al., The potential therapeutic role of interleukin-12 in cutaneous T-cell lymphoma. Ann NY Acad, 1996, 795:310-318.

Verbik et al., In vivo therapeutic effects of interleukin-12 against highly metastatic residual lymphoma. Clin. Exp. Metastasis, 1996, 14:219-229.

(10) Grounds of Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Issue 1

The following ground(s) of rejection are applicable to the appealed claim 1:

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Rook et al. (Clin Exp Immunol, 1997 January, 107 Suppl 1: 16-20). This rejection is set forth in prior Office Action, Paper No. 7, as reiterated herein:

Claim 1 is directed to a method for treatment of advanced cutaneous T cell lymphoma (CTCL) in human with effective amount of recombinant interleukin-12 (IL-12).

Rook discloses that there is deficient interferon-gamma (IFN-γ) production and a marked defect in IL-12 production in advanced cutaneous T cell lymphoma (the abstract, lines 5, and 6-7), and that in vitro studies demonstrate that IL-12 can correct the deficient IFN- γ production and cell-mediated cytotoxicity (the abstract, lines 12-13). Rook further teaches that his experimental results led to phase I/II clinical trials of recombinant IL-12 for treatment of CTCL, wherein IL-12 is administered subcutaneously (page 18, the left column, lines 18-20). Although Rook does not explicitly teach a pharmaceutically acceptable carrier with IL-12 in above method, it is well known in the art that a purified protein agent is virtually always used in combination with other agent(s) (such as dissolving solutions) rather than used as its crystal form alone. The fact that recombinant IL-12 is administered subcutaneously in Rook's method indicates the protein is dissolved. Dissolving solutions, such as water or buffers, constitute "a pharmaceutically acceptable carrier". Therefore, Rook's method anticipates the instant claim 1 as being a method for treatment of CTCL in human using recombinant IL-12 in a pharmaceutically acceptable carrier.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Issue 2

The following ground(s) of rejection are applicable to the appealed claims 1 and 3:

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (Ann NY Acad, 1996, 795:310-318), in view of Verbik et al. (Clin Exp Metastasis, 1996, 14:219-229). This rejection is set forth in prior Office Action, Paper No. 7, as reiterated herein:

Claim 1 is directed to a method for treatment of advanced cutaneous T cell lymphoma (CTCL) in human with effective amount of recombinant interleukin-12 (IL-12). Claim 3 is directed to a composition for treatment of CTCL in human comprising recombinant IL-12 and an adjunct therapeutic agent stimulating interferon-γ (IFN-γ) production, said agent comprising a retinoid, IL-18, interferon-α (IFN-α) or IFN-γ.

Rook reports studies in Sezaay syndrom (SzS), an advanced form of CTCL characterized by a marked depressed IFN-γ production (Th1 cytokine) and excess interleukin-4 (IL-4) and interleukin-5 (IL-5) production (Th2 cytokines) by peripheral blood mononuclear cells (PBMCs), and other immune abnormalities (abstract). Further, the reference discloses that PBMCs from patients with SzS exhibit a marked defect in IL-12 production (Figure 1), which is a potent stimulus for IFN-γ production. By addition of recombinant IL-12 to PBMCs from SzS patients, Rook demonstrates that depressed IFN-γ production is normalized in vitro (Figure 2), indicating a marked defect in IL-12 production by SzS PBMCs may be an important factor in the failure of producing normal amounts of IFN-γ and mediating normal cell-mediated immunity (page 315, lines 9-12 of the second paragraph). Rook clearly suggests that "the implications of possibly restoring nearer normal levels, through the provision of exogenous recombinant IL-12, ... are substantial" (page 315, lines 12-15 of the second paragraph), "the presence of normal *in*

vivo concentrations of both IL-12 and IFN-γ could favor the enhancement of anti-tumor cell-mediated immune responses that are deficient in this disorder" (page 316, lines 3-5), and "in view of the specific immune defects in association with advanced CTCL, along with the poor prognosis of SzS, the institution of controlled trials using recombinant IL-12 alone and with other Th1-inducing agents should be pursued" (page 316, the third paragraph).

Rook did not actually perform such a method of treatment *in vivo*.

Verbik teaches a method for treatment of a murine lymphoma with IL-12 in mice (in vivo). The therapeutic effect of IL-12 was demonstrated by a very significant increase in the overall survival of the treated animals (Figure 1).

With respect to claim 1, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to design a method for treatment of advanced CTCL in a human by administering recombinant IL-12 based upon strong indications taught by Rook (IL-12 deficiency and normalization of IFN-γ by exogenous IL-12 in SzS PBMCs). One of ordinary skill in the art would have been motivated to do so as Verbik teaches strongly toward an expectation of success at treating a lymphoma by administering IL-12 *in vivo*.

Therefore, the art taken as a whole provides motivation to treat an advanced CTCL in a human by administering recombinant IL-12 as suggested by Rook with a reasonable expectation that recombinant IL-12 regiment would be beneficial to these patients as indicated by Verbik's in vivo results.

With respect to claim 3, a composition comprising recombinant IL-12 and a retinoid or IFN-γ is obvious over the same reference for the following reasons: Rook clearly states that "the presence of normal *in vivo* concentrations of *both IL-12 and IFN-γ* could favor the enhancement of anti-tumor cell-medicated immune responses that are deficient in this disorder". Thus, Rook can be interpreted as suggesting co-administering recombinant IL-12 and IFN-γ. Further, Rook clearly suggests a method for treating CTCL using recombinant IL-12 with other Th1-inducing agents (see above), and IFN-γ is a Th1

cytokine. Additionally, Rook teaches that retinoid compounds exert beneficial therapeutic effects for CTCL, and Rook's data indicates that retinoid compounds produce effects on IFN-γ production that should beneficially alter the cytokine "imbalance" in CTCL (page 316, the second paragraph). As IFN-γ is a Th1 cytokine, retinoid compounds are Th1-inducing agents.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a composition comprising recombinant IL-12 and IFN-γ or a retinoid in order to practice the method for treatment of advanced CTCL "using recombinant IL-12 ... with other Th1-inducing agents" suggested by Rook. One of ordinary skill in the art would have been motivated to do so as clearly suggested by Rook, with a reasonable expectation that such combination therapy would be beneficial to these patients because of the functional similarity of IL-12 and IFN-γ or a retinoid, and the potential additive effect of such combination on increasing IFN-γ production, which is known to play a critical role in anti-tumor immune response.

Issue 3

The following ground(s) of rejection are applicable to the appealed claim 3:

Claim 3 is further rejected under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (1996) and Verbik et al. as applied to claims 1 and 3 above, and further in view of Rook et al. (1997). This rejection is set forth in prior Office Action, Paper No. 7, as reiterated herein:

Claim 3 is directed to a composition for treatment of CTCL in human comprising recombinant IL-12 and an adjunct therapeutic agent stimulating interferon-γ (IFN-γ) production, said agent comprising a retinoid, IL-18, interferon-α (IFN-α) or IFN-γ.

The teachings of Rook (1996) and Verbik are reviewed above. Neither Rook (1996) nor Verbik teaches a composition comprising recombinant IL-12 and IL-18, or IFN-α specifically.

Rook (1997) teaches that IFN-α potently suppresses the abnormal IL-4 and IL-5 production (as mentioned above, SzS PBMCs produce excess amount IL-4 and IL-5), and IL-12 appears to exert a small, but consistent inhibitory effect on the excess IL-4. Moreover, this inhibitory effect of IL-12 appears to be additive with the inhibitory effect of IFN-α (page 17, the first and the last paragraphs).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a composition comprising recombinant IL-12 and IFN-α as indicated by Rook et al. (1997) in order to treat advanced CTCL as suggested by Rook's (1996 and 1997). One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success as Rook (1997) teaches strongly the additive effects of the combination treatment with IL-12 and IFN-α.

Issue 4

The following ground(s) of rejection are applicable to the appealed claim 4:

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (Ann NY Acad, 1996, 795:310-318). This rejection is set forth in prior Office Actions, Paper No. 10, as reiterated herein:

Claim 4 is directed to a method for treatment of advanced CTCL in human with effective amount of recombinant interleukin-12 (IL-12) in a pharmaceutically acceptable carrier and an adjunct therapeutic agent stimulating interferon-γ (IFN-γ) production.

Teachings by Rook's reference are reviewed above.

Rook did not actually perform such a method of treatment in vivo (or human).

However, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to design a method as claimed for treatment of advanced CTCL in a human by administering recombinant IL-12 *with* an adjunct therapeutic agent stimulating IFN-γ (Th1 cytokine) production, based upon the strong teachings from Rook's in vitro studies and suggestions, that SzS, an advanced form of CTCL, is characterized with a marked depressed IFN-γ production, and a marked defect in IL-12 production by

PBMCs, and that the presence of normal *in vivo* concentrations of *both* IL-12 and IFN-γ could favor the enhancement of anti-tumor cell-medicated immune responses that are deficient in this disorder. One of ordinary skill in the art would have been motivated to treat human CTCL by administering recombinant IL-12 *with* an adjunct therapeutic agent stimulating IFN-γ production at Rook's suggestion and reasonably would have expected success because such combination would correct both defects of IL-12 and IFN-γ in these patients, thus enhance anti-tumor immune responses.

Although Rook's reference is silent about "a pharmaceutically acceptable carrier" with IL-12 in above method, it is well known in the art that a purified protein agent is usually used in combination with other agent(s) (such as dissolving solutions), and cannot be used as its crystal form alone. The fact that recombinant IL-12 is used in media in Rook's method indicates the protein is dissolved. Dissolving solutions, such as water, buffers, or media, meet the limitation of being "a pharmaceutically acceptable carrier".

(11) Response to Argument

Issue 1

With regard to the rejection of claim 1 under 35 U.S.C. 102(b) over Rook (1997), the essential disagreement appears to be the interpretation of Rook's teaching, what exactly Rook teaches, and whether such teaching is anticipatory.

At page 5 of the brief, appellant indicates that the Examiner has "dismissed" a declaration provided by the inventor and author of the prior art reference (Alain Rook). [as being ineffective to overcome the rejection.] The declaration filed on 6 August 2001 (paper No. 9) under 37 CFR 1.131, was not "dismissed", rather it was *fully considered*, but found ineffective to overcome the Rook reference for the reasons addressed in the subsequent Office Action (paper No. 10), and the examiner stated:

> The declaration filed under 37 CFR 1.131 has been considered but is ineffective to overcome the prior art reference by Rook. The evidence submitted is insufficient to establish a reduction to practice of the invention prior to the effective date of the prior art reference. It is noted that the declaration fails to provide any *evidence* that the clinical efficacy

> of IL-12 was disclosed only after the publication, and it is merely an allegation of such. Therefore, the declaration is insufficient to overcome the reference, in which Rook teaches IL-12 treatment in humans.

Furthermore, the Rook reference is a statutory bar under 35 U.S.C. 102(b) and thus cannot be overcome by an affidavit or declaration under 37 CFR 1.131. Inventor cannot obtain valid patent on known use of known process that has been described in literature more than one year prior to date of invention, in that such processes are old, regardless of relative success of prior and later participants. *Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc.*, 58 USPQ2d 1508 (CA FC 2001).

At pages 5 to 6, appellant argues that nowhere does the Rook paper teach the successful and effective in vivo use of IL-12, either with or without interferon-γ to treat human CTCL, and Rook does not teach treatment in humans. This argument is not persuasive because it states clearly in the Rook reference that phase I/II clinical trials of recombinant IL-12 administered subcutaneously for CTCL had commenced (page 18, lines 18-20 of the left column). As phase I/II clinical trials are performed on humans, this limitation is met. Appellant further argues, at pages 6 to 7, that there is only a single statement in the reference indicating "these studies led to a phase I trial of IL-12 to treat CTCL", no actual data on such a trial are provided or discussed, and the reference fails to provide details of how such a trial would be conducted, and that it was not until after the publication at issue that the clinical efficacy of IL-12 in CTCL patients was discovered and the clinical study had not been performed at the time of the publication, which was stipulated in a declaration filed under 37 CFR 1.131 by the inventor (*note:* the author of the prior art reference is the inventor of the current application). This argument is not persuasive because the reference at least discloses and affirms the clinical application of IL-12 to treat human CTCL (Phase I clinical trial approved by FDA), and further teaches subcutaneous administration, which together meet the limitation of the instant claim 1 directed to a method for treating CTCL in a human by administering recombinant IL-12 in a pharmaceutical acceptable carrier, and one of skill in the art would be able to practice Rook's method by following the teachings in the reference without details of how a trial

would be conducted, as such administration is well known in the art. It is not necessary that actual reduction to practice have occurred, and Rook provides conceptual reduction to practice of administration of recombinant IL-12 to human for treatment of CTCL.

With respect to the argument of efficacy of the treatment (pages 6 to 7), actual efficacy data is not required for anticipation because the reference discloses a method consistent with claim 1, which does not require any specific result to be attained. The claimed method in the instant invention is not directed to a new use, and it is a known method directed to the same use, i.e., treating CTCL patients, as that disclosed in the prior art reference. The instant situation is similar to that addressed in *Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc.,* 58 USPQ2d 1508 (CA FC 2001), in which the prior art reference (the defendant) discloses Phase I clinical trial study, which is directed to a method for treating a cancer patient by administering an anticancer drug, however, the study did not achieve a favorable outcome, i.e., no antitumor efficacy was observed. A subsequent patent application claims the same method with the additional efficacy limitation of "to effect regression of" the tumor. The court expressed the opinion that the prior art reference is anticipatory despite the unfavorable result, and that "expressions of efficacy in claims of patents directed to administration of anticancer drug will not be given limiting effect, even though new uses of old processes are patentable, since claimed process in present case is not directed to new use, and it consists of same steps described in prior art reference, and since newly discovered results of known processes directed to same purpose are inherent, and thus are not patentable". This case differs from the fact situation in *Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc.,* in that in this case, the claims do not state a specific intended result; clearly the Rook reference is anticipatory, consistent with the decision in *Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc.* In addition, in *Celeritas,* 150 F.3d at 1361, 47 USPQ2d at 1522, the court held that "[a] reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference `teaches away' from the invention is inapplicable to an anticipation analysis." Therefore, the efficacy of IL-12 treatment of CTCL is irrelevant as to whether the Rook reference is anticipatory to the current claim, so long as Rook teaches

administration of an amount that achieves a biological effect, such as increase in IFN-γ production, which Rook does. Assuming, in arguendo, that "effective amount" (or efficacy) has bearing on the rejection, and further assuming that Rook did not teach the specific effect of IL-12 on inducing IFN-γ production (which it does), it still would be anticipatory because an amount of IL-12 capable of eliciting any measurable biological effect would meet the claim limitation as the claim merely recites "effective amount" without specifying what effect is.

Furthermore, with respect to the issue that the clinical study had not been performed at the time of the publication, in *Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc.*, (*ibid*), the court held that anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art. Donohue, 766 F.2d at 533, 226 USPQ at 533 ("It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement."). In the instant case, Rook's teaching of phase I/II clinical trials of recombinant IL-12 administered subcutaneously for CTCL confirms the clinical application in humans as these clinical trials must have been approved by FDA, and without further detail, it clearly enables one of skill in the art to practice the method because it discloses a specific agent for a specific disease in a specific species (humans) by a specific route of administration.

At pages 7 to 8 of the brief, appellant further argues that Phase I clinical trials are merely safety studies, usually to healthy volunteers, but sometimes to patients with a disease, and it is not a study of efficacy of a drug, therefore, a mere statement in the prior art reference that a Phase I clinical study is underway is not evidence that FDA has *any* belief that the drug has efficacy for treatment of disease. This argument is not persuasive because, while the Examiner acknowledges that a Phase I clinical study focuses on the safety of a drug, not efficacy, Rook also teaches Phase II clinical trial of recombinant IL-12 administered subcutaneously for CTCL have also commenced (page 18, lines 18-20 of the left column). In addition, Rook teaches that IL-12 induced IFN-γ production, augments natural killer cell cytotoxicity, and cytotoxic T lymphocyte proliferation and function (page

17, the left column, the fourth paragraph, lines 1-6), all of which have important roles in anti-tumor immune response, and can be measured as effective parameters. As there no specific limitations to efficacy in the appealed claim, Rook's teaching meets the limitation of the claim. Additionally, it should be pointed out that a Phase I clinical study for *cancer* therapy uses *patients* with the specific disease as opposed to healthy volunteers. Further, the statement that Phase I clinical study is not evidence that FDA has *any* belief that the drug has efficacy is both irrelevant and inaccurate. Before a drug can enter human clinical trials, the applicant must provide a convincing rationale to FDA that the investigation may be successful. Such a rationale would provide a basis for the applicant's expectation that the investigation may be successful. The FDA approves clinical trials based on a reasonable expectation of success for therapeutic or other clinical applications, and FDA would not simply and randomly approve any drug for a Phase I clinical study without *any* belief in its efficacy even though efficacy is not the focus of Phase I clinical trial. Furthermore, Rook does teach Phase II clinical trial of recombinant IL-12 administered subcutaneously for CTCL have also commenced, which focuses on efficacy of the treatment.

Issue 2

With regard to the rejection of claims 1 and 3 under 35 U.S.C. 103(a) over Rook (1996) and Verbik, the essential issue appears to be whether the combination of cited arts teaches or suggests all the claim limitation, and a reasonable expectation of success, therefore, renders the obviousness of the present invention in claims 1 and 3.

At page 9 of the brief, appellant argues that Rook (1996) does not teach treatment of CTCL in humans using IL-12 either alone or in combination with agents that increase interferon-γ production as claimed in claims 1 and 3 (also at page 11, the third paragraph). At page 10 of the brief, appellant argues that Verbik indicates that the use of IL-12 with other interleukins caused unexplained early deaths in the test mice (lines 2-4), and Verbik believed that it was IL-12 that was leading to unacceptable toxicity (lines 14-16). The appellant further argues that the combination of prior art references fails to meet all three criteria (suggestion or motivation, expectation of success, and suggestion of all the claim

limitation) required by MPEP 2143 to establish a prima facie case of obviousness under 35 U.S.C. 103(a).

With respect to the issue of lack of expectation of success by the references, appellant further argues, in the brief, that neither of the references provides a reasonable expectation of successfully treating CTLL in human with IL-12 alone or in combination with a IFN-γ stimulating agent (page 12, the second paragraph), that Verbik actually puts into question the safe use of IL-12 by showing unexpected toxicity in animals attributed to IL-12 (at page 11, the fourth paragraph), and that the presence of life-threatening toxicity in animals often will lead to not test the compound in humans, therefore, Verbik does not provide a reasonable expectation of success for the method (page 12, lines 4-6), thus, one of skill would refrain from administering IL-12 to humans (page 12, lines 13-14). These arguments are not persuasive for the following reasons: first, as the central issue raised by the appellant is the life-threatening toxicity of IL-12 in animals in Verbik's study, the Examiner would like to clarify the study results by Verbik. The unexplained early death in the test mice was not a consequence of IL-12 treatment, rather, it was resulted from a *combination* treatment of IL-12 *and* IL-2-ASC (page 227, lines 1-7 of the right column, and Figure 3). Similarly, the severe gastrointestinal damage in the experimental animals observed by others and cited by Verbik was a result of a combination of lethal radiation with IL-12 (page 227, lines 17-21 of the right column). It is the appellant's assertion, not Verbik's belief, that it was IL-12 was leading to unacceptable toxicity because there is no such concept is ever stated or suggested in the reference. Contrary to the appellant's assertion, Verbik demonstrates clearly that IL-12 alone exhibits strong in vivo antitumor effect (Figures 1 and 2, and page 223, lines 13-15 of the left column), and *no* early death for IL-12 treated mice comparing to mice in the control group (receiving no IL-12), in which all animals died by day 16, as clearly demonstrated in Figure 1, thus Verbik's teaching provides an undoubted indication for a *reasonable expectation* of success of IL-12 treatment for the human disease. Further, one of skill in the art would not accept extrapolation that the unacceptable toxicity from a combination therapy of IL-12 and IL-2-ASC or lethal radiation was due to IL-12 without further supporting evidence because it is

well known in the art that drug interaction or possible excess synergistic adverse effect between two drugs when used in combination can be toxic and sometimes lethal for the drugs that, otherwise, are safe and therapeutic when used separately. Therefore, one cannot conclude that it was IL-12 was leading to unacceptable toxicity in the absence of supporting evidence, and especially in the presence of Verbik's result demonstrating that IL-12 alone exhibits strong *in vivo* antitumor effect. With respect to the argument that neither of the references provides a reasonable expectation of successfully treating CTCL *in human*, the requirement for a reasonable expectation of success does not rest on a complete certainty of success. Virtually all initial clinical applications are based on in vitro and/or in vivo animal studies, and it is impossible for a pre-clinical trial reference to teach and to ensure the absolute certainty of success in treating human diseases before a human clinical trial. Therefore, a prior art reference only needs to provide an indication of a *reasonable expectation* of success, and the cited combination of prior art references has provided such, as cited above. In particular, the teachings by Verbik that by day 16 all control mice (receiving no IL-12) had died of massive tumor burden in their liver and lungs, no tumor nodules were present in the IL-12 treated mice 60 days post tumor inoculation clearly demonstrate in vivo antitumor properties of IL-12 (page 223, the left column). Further, Rook does teach treatment in humans as indicated that phase I/II clinical trials of recombinant IL-12 administered subcutaneously for CTCL have commenced (page 18, lines 18-20 of the left column), which is a clear indication of a *reasonable expectation* of success because such clinical trials have been approved by the FDA who believes a potential success of the treatment.

With respect to the issue of lack of teaching, suggestion, or motivation by the references, appellant argument that Rook (1996) does not teach treatment of CTCL in humans using IL-12 either alone or in combination with agents that increase interferon-γ production as claimed in claims 1 and 3 (page 9 and 11) is not persuasive because even though Rook did not actually carry out in vivo treatment using IL-12, or administration of IL-12 with an adjunct therapeutic agent, the reference *clearly teaches and suggests* the limitations in claim 3. The reference states that "in view of the specific immune defects in

association with advanced CTCL, along with the poor prognosis of SzS, the institution of controlled *trials* using recombinant *IL-12 alone* and *with other* Th1-inducing agents should be pursued" (page 316, the third paragraph), and that "retinoid compounds exert beneficial therapeutic effects for CTCL", and "as *an adjunct* to the use of cytokine therapy for CTCL, our preliminary data indicate that retinoid appear to produces effects on IFN-γ [Th1 cytokine] production that should beneficially alter the cytokine "imbalance" in CTCL" (page 316, the second paragraph). As addressed above, IFN-γ is a Th1 cytokine, and retinoid compounds are Th1-inducing agents. Therefore, based on Rook's results and suggestion, the person of skill in the art would immediately envision that recombinant IL-12 alone and with other Th1-inducing agents, such as a retinoid compound, would reasonably be expected to therapeutic value in treatment of CTCL in humans.

Issue 3

With regard to the rejection of claim 3 under 35 U.S.C. 103(a) over Rook (1996) and Verbik, and further in view of Rook (1997), the essential issue appears to be whether the combination of cited art teaches or suggests all the claim limitations, and a reasonable expectation of success, therefore, renders the obviousness of the present invention in claim 3.

At page 14 of the brief, appellant argues that Rook (1996) does not teach treatment of CTCL in humans using IL-12 either alone or in combination with agents that increase interferon-γ production as claimed in claim 3 (also at page 18, the last paragraph), and that Verbik indicates that the use of IL-12 with other interleukins caused unexplained early deaths in the test mice (lines 7-9), and Verbik believed that it was IL-12 that was leading to unacceptable toxicity (lines 19-21). At page 15 of the brief, the appellant further argues that Rook (1996) and Verbik fail to provide a teaching of the clinical use of IL-12 either alone or in combination with adjunct therapeutic agents for treating CTCL in humans, and the combination of prior art fails to provide even a reasonable expectation of success in humans in teaching that IL-12 has life-threatening toxicity, a fact that would lead one of skill to question the safe use of IL-12 in humans. These arguments are not persuasive

because, as stated above, Rook (1996) *clearly teaches and suggests* the clinical use of IL-12 either alone or in combination with adjunct therapeutic agents for treating CTCL in humans by stating that "in view of the specific immune defects in association with advanced CTCL, along with the poor prognosis of SzS, the institution of controlled *trials* using recombinant *IL-12 alone* and *with other* Th1-inducing agents should be pursued" (page 316, the third paragraph), and that "as an adjunct to the of cytokine therapy for CTCL, our preliminary data indicate that retinoid appear to produces effects on IFN-γ [Th1 cytokine] production that should beneficially alter the cytokine "imbalance" in CTCL" (page 316, the second paragraph). Therefore, based on Rook's results and suggestion, it is instantly obvious to one of skill in the art that recombinant IL-12 alone and with other Th1-inducing agents, such as a retinoid compound, can have potential therapeutic values in treatment of CTCL in humans. With respect to the life-threatening toxicity disclosed in Verbik reference, the argument is not persuasive for the same reasons addressed above (page XYZ, in issue 2 response). One of skill in the art can not accept the conclusion from a combination therapy of two drugs to be applied to one of them used alone, especially in the presence of evidence that when it was used alone, IL-12 was proven to be safe and effective.

At page 16 of the brief, the appellant argues that in accordance with MPEP 2121.01, the test in determining that quantum of prior art disclosure which is necessary to declare an applicant's invention obvious within section 103, is whether a reference contains an "enabling disclosure", and that Rook (1997) does not teach treatment in humans, it was not until after the publication at issue that the clinical efficacy of IL-12 in CTCL was disclosed. This argument is not persuasive because, in addition to the Examiner's response above at page ABC ("12"), Rook (1997) teaches treatment in humans as indicated that phase I/II clinical trials of recombinant IL-12 administered subcutaneously for CTCL have commenced (page 18, lines 18-20 of the left column), which is also addressed above. More importantly, the claim limitation of treatment of CTCL in a human is merely of an intended use, which does not alter the nature of the composition. Therefore, such claim limitation adds no patentable weight to said

composition. The major issue regarding claim 3 is that Rook (1997) *does* contain an "enabling disclosure" as the reference clearly indicates that IFN-α potently suppresses the abnormal IL-4 and IL-5 production by the CTCL tumor cells, and IL-12, besides its function in promoting IFN-γ production, exerts a small, but consistent inhibitory effect on the excess IL-4, which is additive with the inhibitory effect of IFN-α. Therefore, it would have been instantly obvious to one of skill in the art to make a composition comprising IL-12 and IFN-α, and making a composition as such is well known in the art, and a simple physical admixture of IL-12 and IFN-α in water or buffer would be a composition of claim 3. Absence of a specific teaching of such a well known procedure in the cited prior art does not make it unenabling, and it is not necessary that the references teach that which is notoriously old in the art, such as how to combine two cytokines in solution.

At page 17 of the brief, the appellant further argues that a Phase I trial is underway is not enabling for one of skill to understand that drug being tested has efficacy to treat disease, and accordingly, Rook (1997), when combined with Rook (1996) and Verbik, does not make obvious the instant claim 3 which is drawn to treatment of CTCL. This argument is not persuasive because, as addressed above, the claim limitation of treatment of CTCL in a human is merely of an intended use, as claim 3 is drawn to a composition, not to a method of treatment, such intended use does not alter the nature of the composition. Therefore, such claim limitation adds no patentable weight to said composition. Further, Phase I trial is underway taught by Rook (1997) is enabling because it confirms the clinical application in humans as the clinical trials must have been approved by FDA, and the reference discloses a specific agent for a specific disease in a specific species (humans) by a specific route of administration. Therefore, without further detail as to how a trial would be conducted, which is well known in the art, one of skill in the art would be able to practice the method.

At page 18 of the brief, the appellant argues that the combination of prior art references fails to meet all three criteria (suggestion or motivation, expectation of success,

and suggestion of all the claim limitation) required by MPEP 2143 to establish a prima facie case of obviousness under 35 U.S.C. 103(a).

With respect to the issue of lack of expectation of success by the references, appellant further argues that none of the references provides a reasonable expectation of successfully treating CTLL in human with IL-12 alone or in combination with a IFN-γ stimulating agent, and Verbik actually puts into question the safe use of IL-12 by showing unexpected toxicity in animals attributed to IL-12. This argument is not persuasive because FDA approved Phase I clinical trial in Rook (1997) is a clear indication of a reasonable expectation of success. The appellant stated in the brief, that when a Phase I study is begun, FDA has merely agreed that the drug has been shown to be safe for use in humans based on animal data. However, as addressed above at page XYZ (response to issue 1, the last paragraph), FDA would not have approved any drug simply because of its safety, and FDA must have believed that the drug would have potential therapeutic effect even though the purpose of Phase I is focused on safety, not the efficacy. Furthermore, as addressed above under "Ground of rejection" regarding claim 3, a reasonable expectation of success regarding to claim 3 is suggested by Rook (1997) as that IFN-α potently suppresses the abnormal IL-4 and IL-5 production by the CTCL tumor cells, and IL-12, besides its function in promoting IFN-γ production, exerts a small, but consistent inhibitory effect on the excess IL-4, which is additive with the inhibitory effect of IFN-α. With respect to the argument regarding the toxicity of IL-12, as addressed above, the appellant's interpretation or conclusion from Verbik's results is incorrect for the same reasons addressed above at page XYZ (issue 2 response, the paragraph bridging pages 15 and 16, for now).

With respect to the issue of lack of teaching, suggestion, or motivation, the appellant further argues that Rook (1996) does not teach a method of in vivo treatment using IL-12, and fail to teach administration of IL-12 with an adjunct therapeutic agent as claimed in claim 3; and Rook (1997) does not teach use of IL-12 with an adjunct therapeutic agent in a clinical trial. This argument is not persuasive. In response to

applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The Examiner agrees that each of the reference by itself does not teach all limitations in claim 3. However, the cited references are used in combination to render the claim obvious, not anticipated. The Examiner has repetitively cited the teachings by all three references, and together, they render the claim obvious for the reasons above.

Issue 4

With regard to the rejection of claim 4 under 35 U.S.C. 103(a) over Rook (1996), the essential issue appears to be whether the cited prior art reference teaches or suggests all the claim limitation, and a reasonable expectation of success, therefore, renders the obviousness of the present invention in claim 3.

At pages 20-21 of the brief, the appellant argues that the of prior art references fails to meet all three criteria (suggestion or motivation, expectation of success, and suggestion of all the claim limitation) required by MPEP 2143 to establish a prima facie case of obviousness under 35 U.S.C. 103(a).

At page 21 of the brief, the appellant further argues that Rook (1996) teaches only in vitro culture experiment with PBMCs and a single cytokine, IL-12, does not teach a composition comprising IL-12 with a separate adjunct agent stimulating production of IFN-γ, as claimed in the instant invention of claim 4, and fails to provide reasonable expectation of success. This argument is not persuasive for the following reasons.

With respect to the argument that Rook (1996) does not teach the composition comprising IL-12 with a separate adjunct agent, such composition is not required by claim 4. So long as IL-12 and said agent are administered, the claim limitation is met, and the claim does not mention a composition. Further, even if the claim required the composition, for the same reasons for claim 3 as addressed above, the *suggestion* of such a composition is clearly indicated in the reference as such "in view of the specific immune defects in association with advanced CTCL, along with the poor prognosis of SzS, the institution of controlled *trials* using recombinant IL-12 alone and *with other* Th1-inducing agents should be pursued" (page 316, the third paragraph), and IFN-γ is a Th1 cytokine. With further exemplification of retinoid compounds, the reference provides specific adjunct therapeutic agent to be used in combination with IL-12 for the treatment of CTCL. With respect to the issue of expectation of success, Rook (1996) demonstrated that both IL-12 and retinoid (Th1- or IFN-γ-inducing agent) stimulate IFN-γ production, which is an indication of *reasonable* expectation of success as additive effect on stimulating IFN-γ production using the combined agents would be expected. Even though Rook did not actually use the combination of IL-12 and an IFN-γ stimulating agent to prove the effectiveness of such, *reasonable* expectation of success is not an equivalent of absolute predictability. Therefore, based on Rook's results and suggestion, it is instantly obvious to one of skill in the art that recombinant IL-12 with other Th1-inducing agents, such as a retinoid compound, can have potential therapeutic values in treatment of CTCL in humans.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Dong Jiang
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